

REMARKS

Claims 12-17, 20-26, and 29 are currently pending in this application. Applicants submit that these claims are in condition for allowance. Applicants wish to thank the Examiner and his supervisor for the courtesies extended to their representative, Cheryl Liljestrand, in an interview conducted on September 15, 2000. At that interview, the Office contended that compounds 1 and 2 were merely exhibiting an additive effect and, therefore, concluded that the claims were obvious in view of U.S. Patent No. 4,965,276 (the "278 patent"). The Office stated in the Interview Summary that "a showing of synergism [was] needed to put the application in condition for allowance."

Applicants contend that the data presented in Table 1 at page 8 of the specification does show just such synergism of action between compound 1 and compound 2. Initially, it should be noted that compound 2, (N-(4-trifluoromethylphenyl)-2-cyano-3-hydroxycrotonic acid amide), is the metabolite of compound 1, (5-methyl-4'-trifluoromethyl-4-isoxazolecarboxanilide), and compounds 1 and 2 are of similar molecular weight. When one observes that the total mg/kg of rat for the first four rows are the same, i.e., 10 mg/kg (and the same is true for the last three rows, i.e., 5 mg/kg), it becomes clear that these compounds are exhibiting a synergistic effect rather than an additive effect.

When 10 mg/kg of compound 1 ("#1") alone is administered, a 74% decrease in paw volume is observed. However, when a total of 10 mg/kg consisting of both #1 and compound 2 ("#2") is administered, the decrease in paw volume jumps dramatically to between 93-95% (see page 8, lines 7-9 for three different combinations ranging from 0.1 to 1.0 mg/kg of #2 and 9.9 to 9.0 of #1). This is more than a 25% change in the

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decrease in paw volume over the same 10 mg/kg of compound 1 alone. This is clearly a synergistic effect. If this were merely an additive effect, there would be a significant difference between the 10 mg/kg combination of 9.0 mg/kg #1 + 1.0 mg/kg #2 and the 10 mg/kg combination of 9.9 mg/kg #1 + 0.1 mg/kg #2, because the amount of #2 differs 10 fold between these two combinations.

This synergistic effect is even more dramatic at the 5 mg/kg level. When 5 mg/kg of compound 1 alone is administered, there is a 10% **increase** in paw volume. However, when a 5 mg/kg (4.85 mg/kg of #1 + 0.15 mg/kg of #2) combination is administered it results in a 10% **decrease** in paw volume. This decrease in paw volume jumps to 46% when the 5 mg/kg (4.5 mg/kg of #1 + 0.5 mg/kg of #2) combination is administered.

Turning to the rejection under 35 U.S.C. § 103(a), a skilled artisan looking at Table 1 of the prior art '276 patent would not conclude that compounds 1 and 2 exhibit a synergistic effect when combined. Instead, one skilled in the art notes that 5 mg/kg of compound 1 alone results in a 4% inhibition and when 10 mg/kg #1 is administered the inhibition drops to 0%. The artisan learns that it requires at least 28 mg/kg of compound 1 to get an inhibition of 92%. No amount of compound 2 was administered.

In Table 2, similar results are observed for concentrations of compound 1 less than 20 mg/kg. There is no data for the combination of compound 1 and 2 in these tables, much less a showing of synergism.

In view of these remarks, Applicants submit that evidence of synergism has been presented in Table 1 of the instant application. This synergism was not obvious from

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the teachings of the prior art '276 patent. Therefore, the rejection under 35 U.S.C. § 103(a) should be withdrawn and the claims allowed.

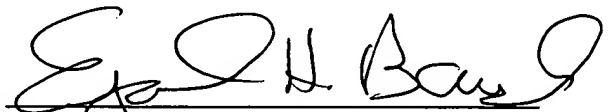
Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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